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EDITORIAL HIGHLIGHT

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A sugar-coated strategy to treat a rare neurologic disease provides a blueprint for a decoy glycan therapeutic and a potential vaccine for CoViD-19

An Editorial Highlight for "Selective inhibition of anti-MAG IgM autoantibody binding to myelin by an antigen specific glycopolymer"on page 486.

Lawrence Steinman

Departments of Pediatrics and Neurology and Neurological Sciences, Stanford University, Stanford, CA, USA

Correspondence
Lawrence Steinman, Departments of Pediatrics and Neurology and Neurological Sciences, Stanford University, Stanford, CA, USA.
Email: steinman@stanford.edu

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Abstract

In a rare neurologic disease known as IgM monoclonal gammopathy the immune system targets a sulfated trisaccharide known as the Human Natural Killer-1 (HNK-1) epitope that comprises a constituent of the myelin sheath known as MAG (myelin-associated glycoprotein). This Editorial highlights a study by Aliu and colleagues in the current issue of the Journal of Neurochemistry, in which the investigators constructed a biodegradable poly-l-lysine backbone with multiple copies of this sulfated HNK-1 trisaccharide. This decoy, poly(phenyl disodium 3-*O*-sulfo-β-D-glucopyranuronate)-(1→3)-β-D-galactopyranoside, known as PPSGG, removed anti-MAG IgM autoantibodies from the blood, while not activating the immune system. These findings provide a path for the selective removal of a pathogenic set of antibodies that target the myelin sheath resulting in neuropathy. These findings are applicable to a parallel strategy for the generation of polysaccharides similar to those present in the receptor-binding domain of CoViD-19, which might inhibit viral adhesion to its receptor, the angiotensin-converting enzyme-2 (ACE2) protein, thereby impairing cellular uptake of the virus itself. The deployment of complex polysaccharides that mimic actual COVID19 polysaccharides on the spike protein may also provide a feasible structural basis for a vaccine. Carbohydrate mimics, if conjugated to a carrier or backbone, might provoke an immune response to the spike protein. A vaccine that targets critical carbohydrates on COVID19, and then neutralizes the virus would recapitulate a successful strategy employed in other microbial vaccines, like the pneumococcal vaccines and the meningococcal vaccines. These vaccines direct an immune response to complex carbohydrates and successfully prevent life-threatening disease. This paper provides lessons from a rare neurologic disease that may teach us strategies applicable to a global pandemic.

KEYWORDS

covid-19, vaccination, monoclonal gammopathy, inflammatory neuropathy, carbohydrate

1 | INTRODUCTION

A demyelinating neuropathy targeting myelin-associated glycoprotein (MAG) has an incidence of approximately one per 100,000 (Mygland & Monstad, 2001). In this disease there is production of an IgM antibody resulting in a "monoclonal gammopathy" targeting a particular carbohydrate known as Cellular Differentiation antigen 57 (CD57) and also known as human natural killer cell-1 (HNK-1). The HNK-1 antigen is found on MAG, as well as on natural killer cells, neuroectodermal tissue, retina, brain, prostate and renal proximal tubules (Pernick, 2019). CD57 belongs to a family of sialic acid-binding Ig-like lectins (siglecs) found on both peripheral and central nervous system myelin.

In this issue investigators (Aliu et al, 2020) showed that poly(phenyl disodium 3-*O*-sulfo-β-D-glucopyranuronate)-(1→3)-β-D-galactopyranoside, known as PPSGG, removed anti-MAG IgM autoantibodies from the blood in a mouse model of this IgM neuropathy. In a previous study these investigators developed antigen-specific molecules with nanomolar inhibitory potency for anti-MAG IgM (Herrendorff et al., 2017). Here the investigators also show that PPSGG blocked the binding of an anti-MAG IgM from patients to sciatic nerve myelin of non-human primates. They also tested some of the pharmacokinetic and pharmacodynamic properties of PPSGG.

In patients suffering from this IgM monoclonal gammopathy, non-specific strategies are used to diminish IgM antibody including targeting of all CD20 B cells with Rituximab. On occasion flares of disease occur with increased IgM levels of antibody targeting MAG have followed therapy with Rituximab (Broglio and Luria, 2005). The strategy employed with PPSGG is specific to the antigen that triggers the pathogenic IgM in this disease. One can refer to such treatment as "antigen-specific" immunotherapy (Figure 1).

Investigations in the mouse model revealed that practical doses of PPSGG were able to sufficiently reduce IgM that binds to MAG. Doses between 1 and 10 μg were sufficient to remove between 23 and 93% of IgM anti-MAG antibody from blood in the mouse model. Reductions in antibody were sustained for as long as 96 hr, demonstrating the pharmacologic feasibility of this highly specific therapeutic approach. In addition the investigators showed that after exposure to PPSGG, there was no activation of B cells, including human IgM anti-MAG B cells. In addition, no activation of CD11b dendritic cells was observed. These experiments provide some assurance on the safety of this approach, if it is translated to human clinical trials. Engaging IgM targeting MAG with PPSGG appeared safe and effective in the pre-clinical study.

Writing about these exquisite approaches to targeting carbohydrates for a potential antigen-specific therapy for an inflammatory

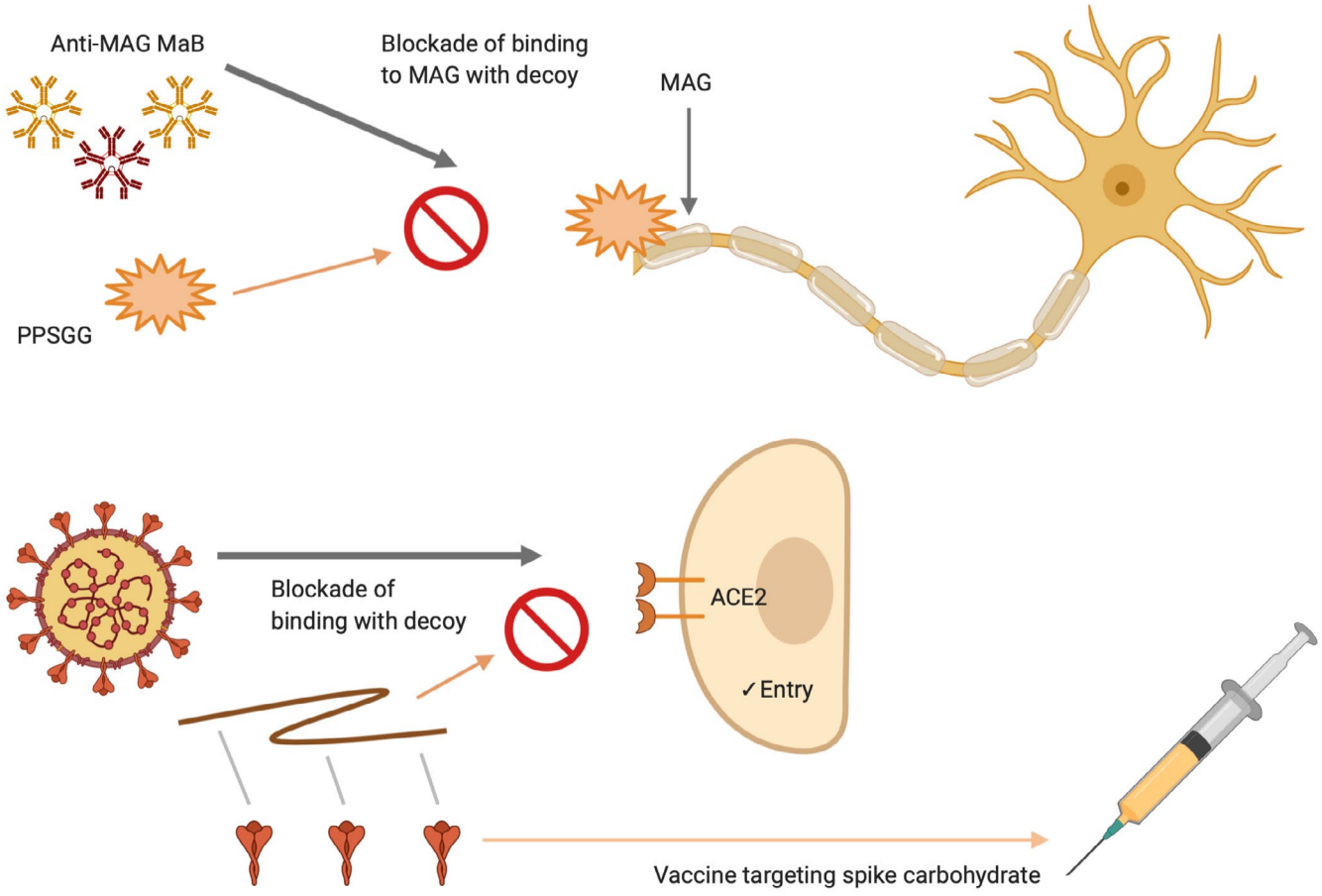

FIGURE 1 The strategy employed by Aliu et al, provide a basis for a passive immune therapy with a decoy carbohydrate preventing the virus from docking on its receptor, and also provide a foundation for a carbohydrate-based active immunization when coupled to a suitable carrier

neuropathy characterized by sensory impairment, disturbance in gait, tremor, and ataxia (a form of incoordination following sensory loss) makes one wonder: *Could such an approach, targeting critical carbohydrates in a disease, have broader applicability to other diseases where complex carbohydrates play a key pathophysiologic role?* In these days of the COVID-19 pandemic, the experiments described on monoclonal IgM neuropathy raise the issue that a similar strategy might be deployed to target the carbohydrates in the spike protein of COVID-19.

Spike proteins in coronviruses are known to be camouflaged by glycans: Mass spectrometry studies revealed in a feline coronavirus that high mannose and complex N-Glycans accounted for a quarter of the mass of the spike. Moreover, the N-glycans are critical for providing the propeller like conformation of these structures (Yang et al., 2020).

In the so-called receptor-binding domain of the spike protein there are 22 glycan-binding sites (Shahajan, Supekar et al. 2020). High mannose, hybrid and complex-type glycans across the N-glycosylation sites have been identified with mass spectrometry. One could imagine building a therapeutic which might contain the carbohydrates, or a suitable mimic, of the spike protein coupled to a carrier molecule, much in a similar fashion to how PPSGG was constructed. Such a "decoy" carbohydrate could block the binding and subsequent internalization of COViD-19 to its receptor, angiotensin converting enzyme-2 (ACE2). In addition, spike carbohydrate clusters coupled to a carrier might proof to be an effective vaccine. Both the pneumococcal vaccine and the meningococcal vaccines target polysaccharides in pneumococcus and meningococcus, respectively. They couple the appropriate polysaccharide to a suitable carrier to achieve potent carbohydrate-specific immunogenicity.

In a different neuroinflammatory disease antibodies to cryptic mannose containing glycans were observed in the cerebrospinal fluid of individuals with multiple sclerosis, and in its animal model EAE (Wang et al., 2014). There again is some precedent for an antigen-specific therapy for an inflammatory disease. Injection of these oligomannose glycans coupled to a protein carrier reduced the clinical severity of paralysis in this animal model (Wang, Bhat et al. 2014). The success in parlaying the oligomannose glycans in MS and in its EAE model, could be emulated in strategies for therapy of COVID-19.

IgM monoclonal gammopathy targeting MAG is indeed a rare disease. Lessons from rare diseases often inform us of bold approaches for the treatment of widespread disease. The pioneering work of Aliu and colleagues described in this issue, might serve as a guidepost for designing effective therapeutics to the glycan components of the COVID19 virus. Such endeavors may produce a sweet ending to a tragedy including both the harsh clinical realities of IgM MAG neuropathy and to the horrors of the deadly CoVID-19 pandemic.

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CONFLICTS OF INTEREST

The author has no conflict of interest to declare.

ORCID

Lawrence Steinman https://orcid.org/0000-0002-2437-2250

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